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*Paltov Ye. V., Masna Z. Z., Chelpanova I. V., Fik V. B., Rudnytska Kh. I., Yuzuch O. V.***STATISTICAL CHARACTERISTICS OF THE COMPONENTS OF COAGULATION HEMOSTASIS AND BLOOD OXYGENATION OF RATS WITH EXPERIMENTAL OPIOID INFLUENCE ON THE EARLY STAGES OF CORRECTION****Danylo Halytsky Lviv National Medical University (Lviv, Ukraine)****kristinarudnytska@gmail.com**

Prolonged use of opioid analgesics for the correction of chronic pain has a toxic effect on the organism. Despite a significant number of scientific reports on the effect of opioid drugs on the organs and systems of the body in experimental studies, there is little data in the modern professional literature on the dynamics of changes in blood parameters when using opioids in the early stages of correction during their withdrawal. The purpose of the study is to establish indicators of coagulation hemostasis and the degree of blood oxygenation in the early stages of opioid exposure during its withdrawal with subsequent correction.

Research material: 78 white, sexually mature outbred male rats weighing 160-200 grams, which were injected intramuscularly with the drug "Nalbuphine" for 42 days. The number of platelets, prothrombin time, prothrombin index, recalcification time, total fibrinogen, hemoglobin, hematocrit value were determined in the blood of experimental animals.

The obtained data were tested for normality using the Shapiro-Wilk test. The non-parametric Kruskal-Wallis H test for three or more independent groups was used to determine the significance of the difference between groups, followed by post hoc analysis using Dunn's test. R v 4.0.3 and RStudio v 1.2.5042 software were used to perform statistical calculations.

At the 6th week, there were changes in the "withdrawal + pentoxifylline" subgroup – the values of this subgroup were as close as possible to the values of the corresponding indicators of the control group. The exception was the indicator of total fibrinogen – its value was lower in the "cancellation" subgroup. For the "pentoxifylline + nalbuphine" subgroup, the biggest difference in indicators compared to the control group was relative to the values of the indicators of the "cancellation" and "cancellation + pentoxifylline" subgroups, excluding platelets and blood hematocrit indicators – for these indicators, the value of the "pentoxifylline + nalbuphine" subgroup was close to the values of the corresponding indicators of the "cancellation + pentoxifylline" subgroup.

Key words: *coagulation hemostasis, blood oxygenation, Nalbuphine, rat.*

Connection of the publication with planned research works. The results of the article correspond to the research plan of Danylo Halytsky Lviv National Medical University and are part of the scientific work of the Normal Anatomy Department and Operative Surgery and Topographic Anatomy Department «Morphofunctional features of organs in the pre – and postnatal periods of ontogenesis, under the influence of opioids, food additives, reconstructive surgery and obesity» (state registration number 0120U002129).

Introduction. According to the European Monitoring Center for Drugs and Drug Addiction, the number of people in the European region who use drugs at least once a year was about 275 million or about 5.6% of the world's population aged 15-64 [1, 2]. In the structure of indicators of the prevalence of mental and behavioral disorders, mental and behavioral disorders as a result of the psychoactive drug use were in the first place (dispensary and preventive supervision groups). This is 41.7%, or 694,928 people, 1,631.6 per 100,000 population [1, 3].

In Ukraine, according to the latest biobehavioral study, the estimated number of people who inject drugs was 317 000 (in the controlled territory of Ukraine), of whom opioid users alone – 200 661 people (63.3% of the total), 38 674 people – consumers of stimulants (12.2% of the total), 77 665 people practiced mixed drugs use (24.5%) [3, 4, 5, 6, 7].

In recent years, in domestic and foreign literature sources, there are more and more publications on

structural changes in the organs under the influence of opioid drugs in an experimental studies [8, 9, 10, 11, 12, 13]. In particular, scientific professional publications cover data on the pathology of the visual organ structures, which relates to the iris – corneal angle [14, 15, 16, 17, 18, 19].

There are still a number of questions concerning the smoothness and depth of opioid angioretinopathy manifestations with changes in blood rheology (platelet count, prothrombin time, prothrombin index, recalcification time of stabilized blood, total fibrinogen, determination of hemoglobin, hematocrit) on different terms of experimental opioid influence and their relationship with the appearance and subsequent progression of angioretinopathy. In particular, the question of correlation of angioretinopathy with rheological parameters of blood (platelet count, prothrombin time, prothrombin index, recalcification time of stabilized blood, total fibrinogen, hemoglobin determination, hematocrit) is still unclear on early and late stages of correction of experimental opioid angioretinopathy.

Given the above, we believe that this study is relevant both in terms of experimental morphology and in terms of practical ophthalmology.

Purpose of the study is to establish indicators of coagulation hemostasis and the degree of blood oxygenation in the early stages of opioid exposure during its withdrawal with subsequent correction.

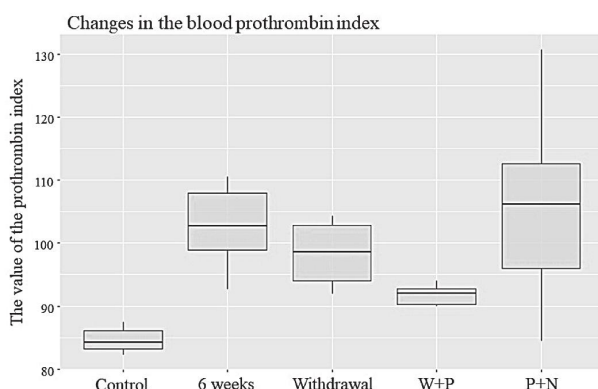


Figure 1 – Indicator of change in prothrombin index after correction during 3rd, 4th, 5th and 6th weeks of opioid exposure.

Object and methods of research. The material of the study were sexually mature, outbred male rats in the quantity of 78 animals, weighing 160-200 g, age 4.5-6.5 months. Animals were injected intramuscularly with nalbuphine once a day in the same time period (10-11 am) for 42 days. The initial dose of nalbuphine during the first two weeks (I-II weeks) was 0.212 mg/kg, the next 2 (II-IV weeks) – 0.225 mg/kg, the next (IV-VI weeks) – 0.252 mg/kg. Thus, conditions for chronic opioid influence were created [20].

Animals were divided into 5 groups: I group of animals received nalbuphine for 42 days, followed by material collection (end of 6th week of experimental opioid exposure); II – control group, which for 42 days received injections of saline intramuscularly in the same time period (10-11 am); III group (2 weeks of nalbuphine injection followed by its withdrawal during 4 weeks); IV group (2 weeks of nalbuphine injection with the addition of pentoxifylline during 4 weeks); V group (2 weeks of opioid injection with its withdrawal followed by pentoxifylline administration for 4 weeks). The correction was performed in the early stages where the dose of pentoxifylline was 2.857 mg/kg. All animals were kept in a vivarium and work on keeping, care, labeling and all other manipulations were carried out in compliance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” [Strasbourg, 1985], “General ethical principles of experiments on animals”, approved by the First National

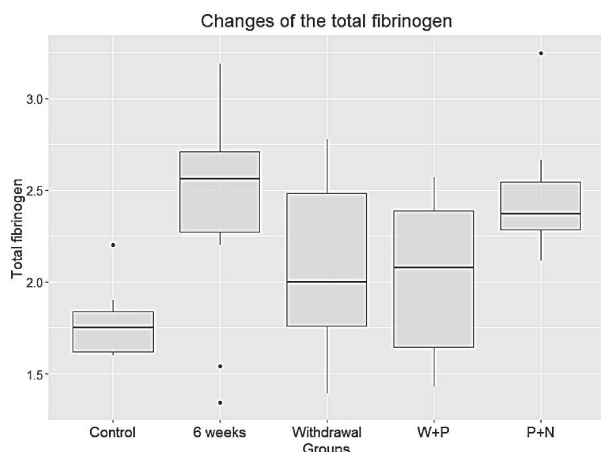


Figure 3 – Indicator of changes in total fibrinogen after correction during 3rd, 4th, 5th and 6th weeks of opioid exposure.

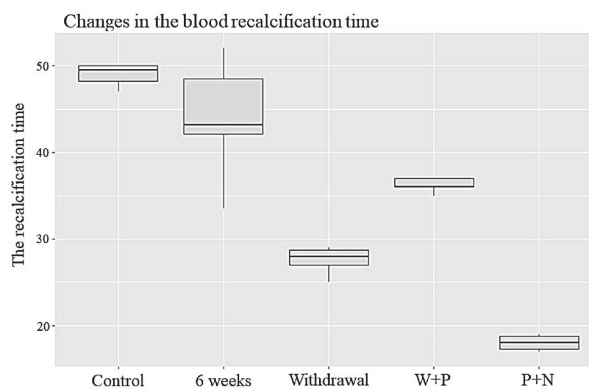


Figure 2 – Indicator of change in recalcification time during correction during 3rd, 4th, 5th and 6th weeks of opioid exposure.

Congress of Bioethics [Kyiv, 2001]. The Commission on Bioethics of Danylo Halytsky Lviv National Medical University established that the conducted research meets ethical requirements according to the order of the Ministry of Health of Ukraine № 231 of 01.11.2000 (Protocol № 10 of 26.12.2011). Blood sampling and study of hematological parameters of blood (platelet count, prothrombin time, prothrombin index, recalcification time of stabilized blood, total fibrinogen, determination of hemoglobin, hematocrit) were performed according to conventional methods [21].

At the first stage of statistical analysis, all the results of studies of blood parameters of animals were tested for normalcy using the Shapiro – Wilk test. According to the results of calculation of this criterion, as well as taking into account the small sample size and discrete nature of the data due to the peculiarities of laboratory methods used to obtain these data, the median and quartile in Me format were used for their presentation [25%; 75%], where Me is the median (50th percentile), 25% is the first quartile (25th percentile), 75% is the third quartile (75th percentile) [22]. In the tables it was additionally indicated the minimum and maximum values of the sample. Boxplots were used for graphical representation, the central line of which indicated the median, the boundaries of the box were quartiles, the mustache was 1.5 range from the corresponding quartile and the points were emissions (values outside the 1.5 range) [23]. Also, a nonparametric Craskel-Wallis test for three or more independent groups was used to determine the significance of the difference between the groups, followed by post-hawk analysis using the Dunn’s test. In order to better interpret the obtained

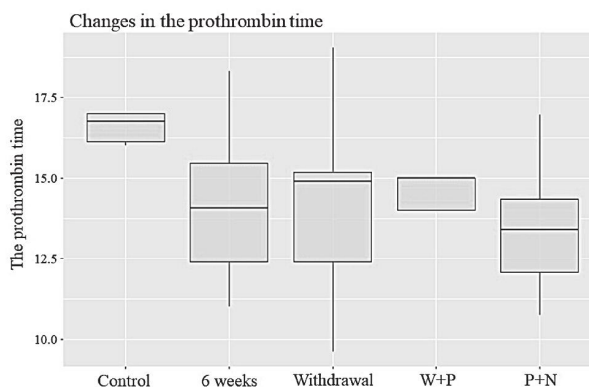


Figure 4 – Indicator of changes in prothrombin time during correction during 3rd, 4th, 5th and 6th weeks of opioid exposure.

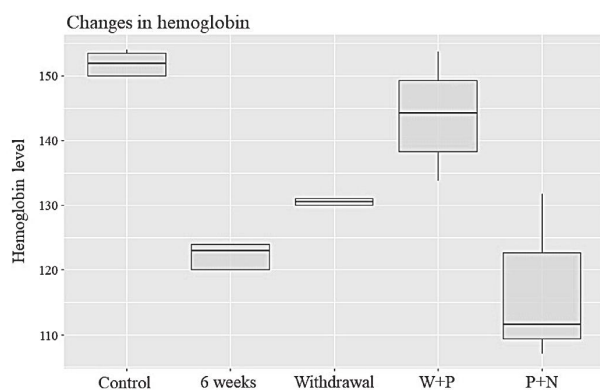


Figure 5 – Indicator of hemoglobin change during correction during 3rd, 4th, 5th and 6th weeks of opioid exposure.

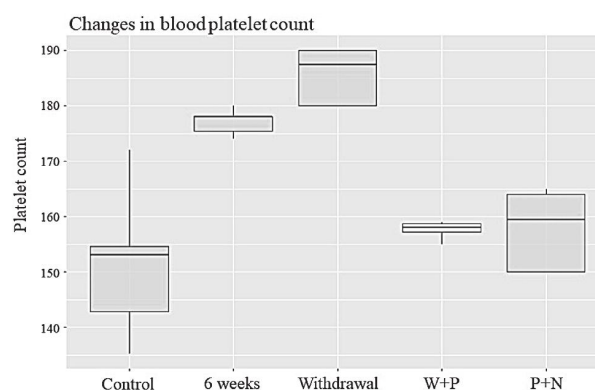


Figure 6 – Indicator of platelet change during correction during 3rd, 4th, 5th and 6th weeks of opioid exposure.

data and compare different indicators of animal blood in the dynamics of the experiment, linear graphs of decimal logarithms of the median values were used.

Software R v 4.0.3 and RStudio v 1.2.5042 were used for statistical calculations and graphing [24, 25]. MSOffice Excel 2010 spreadsheets were used to generate the final tables and store the data.

Research results and their discussion. Based on the hematological examination of the blood of the experimental group of rats in subchronic and chronic periods of exposure to opioid analgesics with subsequent correction with pentoxifylline, the following indicators were established: prothrombin index level, recalcification time, total fibrinogen, prothrombin time, platelet count, hematocrit and hemoglobin level. As a result of our correction in the period of 3rd, 4th, 5th and 6th weeks of opioid exposure, the blood **prothrombin index** of rats of subgroups at 6th week was higher than the control group and ranged within the value of the prothrombin index of the general group at this time, without statistically significant difference compared to it. The minimum value of the prothrombin index was in the subgroup «Withdrawal + pentoxifylline» – 92.00 [90.25; 92.75], thus approaching almost the value of the control group – 84.25 [83.19; 86.10] (the difference is not significant, $p=0.23$) (fig. 1).

The duration of recalcification time in all subgroups of the 6th week of the experiment was lower than the value of the control group and the value of this indicator in the general group. Indicators of the subgroups «pentoxifylline + nalbuphine» and «withdrawal» were minimal and amounted to 18.00 [17.25; 18.75] and 28.00 [27.00; 28.75], respectively, which was significantly less than the control group and the general group of 6 week. At the same time, the recalcification time of the subgroup « withdrawal + pentoxifylline» was close to the value of the general group and was 36.00 [36.00; 37.00] (fig. 2).

The **total fibrinogen** in the subgroups at the 6th week of the study ranged between the control group and the general group. The maximum in the subgroups was the value of the subgroup «pentoxifylline + nalbuphine» – 2.37 [2.28; 2.55]. However, it did not reach the value of the general group (fig. 3).

The **prothrombin time** of blood of rats in subgroups at 6th week remained within the value of prothrombin time of the general group and vary slightly from 13.41 [12.08; 14.34] in the group «pentoxifylline +

nalbuphine» up to a maximum of 15.00 [14.00; 15.00] in the subgroup « withdrawal + pentoxifylline». All indicators in the subgroups were significantly lower than the value of this indicator in the control group and were not significantly different from the value in the general group (fig. 4).

The value of **hemoglobin** in the subgroups «withdrawal» and «pentoxifylline + nalbuphine» was significantly less than the control group and close to the level of the general group and was 130.50 [130.00; 131.00] and 111.59 [109.38; 122.66] respectively. At the same time, the level of hemoglobin of the subgroup « withdrawal + pentoxifylline» at this time of the study was as close as possible to the value of the control group and was 144.23 [138.28; 149.34] (fig. 5).

The number of blood **platelets** in the subgroups « withdrawal + pentoxifylline» and «pentoxifylline + nalbuphine» was close to that of the control group and amounted to 158.00 [157.25; 158.75] and 159.50 [150.00; 164.00], respectively (control group 153.05 [142.91; 154.64], $p=1$). However, the number of platelets in the subgroup «withdrawal» was 187.50 [180.00; 190.00], which was significantly higher than the control group ($p<0.001$) and slightly higher than the general group of the 6th week – 178.00 [175.50; 178.00] ($p=0.56$) (fig. 6).

The **hematocrit** value of rats in the subgroups « withdrawal + pentoxifylline» and «pentoxifylline + nalbuphine» was 38.00 [36.00; 38.00] and 38.00 [37.00; 38.00] respectively and was close to the indicator of the control group – 42.07 [40.13; 43.75], and to the indicator of the general group of the 6th week – 34.00

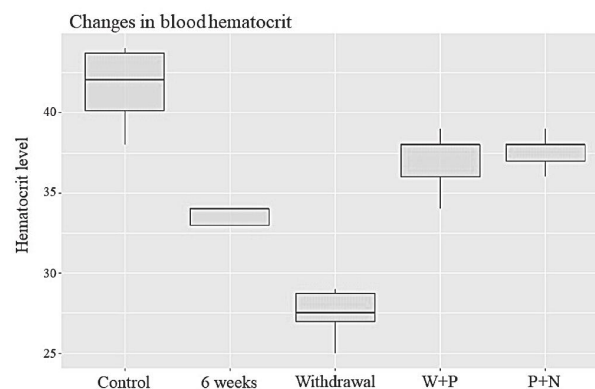


Figure 7 – Indicator of hematocrit change during correction during 3rd, 4th, 5th and 6th weeks of opioid exposure.

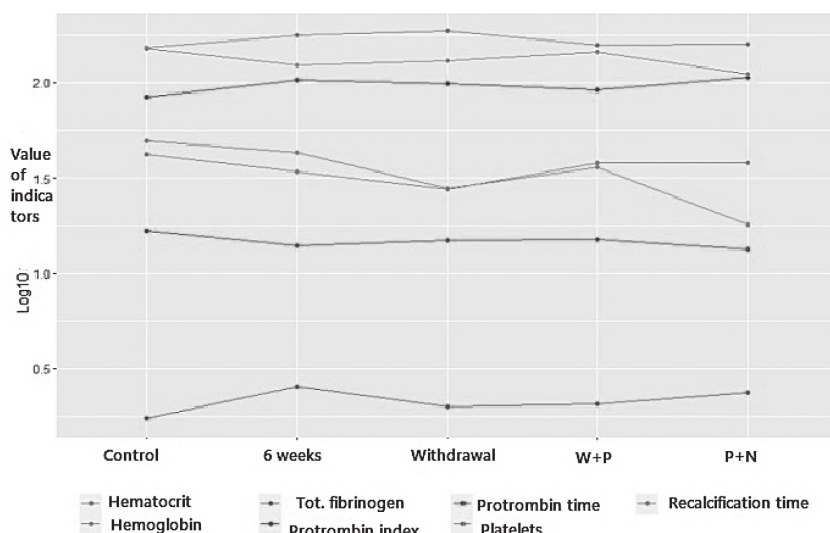


Figure 8 – Generalization of dynamics of changes of indicators at correction during 3rd, 4th, 5th and 6th weeks of opioid influence.

[33.00; 34.00]. The value of blood hematocrit in rats of the subgroup «withdrawal» at this time was minimal among the subgroups being compared and was 27.50 [27.00; 28.75], which was significantly less than the control group ($p < 0,001$) (fig. 7).

In order to compare the changes in all blood parameters of experimental animals in the dynamics, we constructed a linear graph of the values of the decimal logarithms of the median indicators (fig. 8).

Conclusions. More systematic at the 6th week were changes in the subgroup « withdrawal + pentoxifylline» – the values of the indicators of this subgroup in most cases were as close as possible to the values

of the corresponding indicators of the control group. The only exception was the rate of total blood fibrinogen – here the value was slightly lower in the subgroup «withdrawal». The subgroup «pentoxifylline + nalbuphine» was characterized by the biggest difference in indicators compared with the control group relative to the values of the subgroups «withdrawal» and « withdrawal + pentoxifylline» excluding indicators of platelets and blood hematocrit – the value of these indicators in the subgroup «pentoxifylline» + nalbuphine” was close to the value of the corresponding indicators of the subgroup « withdrawal + pentoxifylline». Variation in the values of indicators in the subgroup

«withdrawal» were not systemic. It should be noted that in most cases, variation in the values of indicators in the subgroups at the 6th week were not proven statistically, so they can be interpreted only as tendential, but not proven by relevant criteria.

Prospects for further research. Our study of the correction of indicators of coagulation hemostasis and the degree of blood oxygenation is a basic morphological substrate, which in the future will provide an opportunity to conduct and evaluate a similar correction in the distant terms of opioid influence and compare the data obtained regarding the corrective effect of these indicators in dynamics.

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СТАТИСТИЧНА ХАРАКТЕРИСТИКА КОМПОНЕНТІВ КОАГУЛЯЦІЙНОГО ГЕМОСТАЗУ ТА ОКСИГЕНАЦІЇ КРОВІ ЩУРІВ ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ ОПІОЇДНОМУ ВПЛИВІ НА РАННІХ ТЕРМІНАХ КОРЕКЦІЇ

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Резюме. Велика кількість зовнішніх токсичних чинників сприяє виникненню порушення гематологічного та біохімічного статусу організму. Відомо, що вільнорадикальне окиснення відіграє важливу роль у підтримці транспорту електронів у дихальному ланцюзі, індукції утворення пор у мітохондріальній мембрані, які регулюють спряження дихання з окисним фосфорилуванням і лежить в основі окисних процесів у мітохондріях. Окисні процеси за участю активованих кисневих метаболітів це невід'ємна частина існування вищих форм живих організмів. Встановлено, що при екстремальних впливах в організмі активуються окисно-відновні процеси, які ведуть до утворення ліпо – і гідропероксидів, подальше розкладання яких сприяє утворенню ендogenous кисню, необхідного для життєдіяльності. Супероксид є одним із основних прооксидантів у клітині, тому супероксиддисмутаза відіграє ключову роль у антиоксидантному захисті організму. Функція каталази полягає у руйнуванні токсичного пероксиду водню, який утворюється в процесі різних окисних реакцій в організмі. Дані процеси безпосередньо впливають на показники коагуляційного гемостазу та на ступінь оксигенації крові, пропускаючи каскад біохімічних та гематологічних зрушень, що впливають на розвиток патоморфологічних змін у ланках гемомікроциркуляторного русла та сприяють порушенню показників нормальної гемодинаміки.

Мета дослідження – встановити показники коагуляційного гемостазу та ступеня оксигенації крові на ранніх термінах опіоїдного впливу при його відміні з подальшою корекцією.

При проведенні нашого дослідження було використано 78 білих статевозрілих безпородних щурів-самців, масою 160-200 грам, яким впродовж 42 діб проводили дом'язово ін'єкції препарату "Налбуфін". У крові експериментальних тварин на різних термінах опіоїдного впливу визначали кількість тромбоцитів, протромбіновий час, протромбіновий індекс, час рекальцифікації, загальний фібрिनотен, гемоглобін та гематокритну величину.

Отримані дані проходили перевірку на нормальність із використанням критерію Шапіро-Уїлка. Для визначення достовірності різниці між групами було використано непараметричний критерій Н Краскела-Уолліса для трьох та більше незалежних груп із подальшим пост-хок аналізом із використанням тесту Дана. Для проведення статистичних обрахунків використовували програмне забезпечення R v 4.0.3 та RStudio v 1.2.5042.

На шостому тижні зміни у підгрупі корекція «відміна + пентоксифілін» – за значенням показників були максимально наближеними до значень відповідних показників контрольної групи.

Ключові слова: коагуляційний гемостаз, оксигенація крові, налбуфін, щур.

STATISTICAL CHARACTERISTICS OF THE COMPONENTS OF COAGULATION HEMOSTASIS AND BLOOD OXYGENATION OF RATS WITH EXPERIMENTAL OPIOID INFLUENCE ON THE EARLY STAGES OF CORRECTION.

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Abstract. A large number of external toxic factors contribute to the occurrence of a violation in hematological and biochemical status of the body. It is known that free radical oxidation plays an important role in maintaining the transport of electrons in the respiratory chain, inducing the formation of pores in the mitochondrial membrane, which regulate the coupling of respiration with oxidative phosphorylation and is the basis of oxidative processes in mitochondria. Oxidative processes involving activated oxygen metabolites are an integral part of the existence of higher forms of living organisms. It has been established that under extreme influences in the body, redox processes are activated, which lead to the formation of lipo – and hydroperoxides, the further decomposition of which contributes to the formation of endogenous oxygen, necessary for life. Superoxide is one of the main pro-oxidants in the cell, so superoxide dismutase plays a key role in the body's antioxidant defense. The function of catalase consists in the destruction of toxic hydrogen peroxide, which is formed in the process of various oxidative reactions in the body. These processes directly affect the indicators of coagulation hemostasis and the degree of blood oxygenation, triggering a cascade of biochemical and hematological changes that affect the development of pathomorphological changes in the links of the hemomicrocirculatory channel and contribute to the violation of normal hemodynamic indicators.

The purpose of the study is to establish indicators of coagulation hemostasis and the degree of blood oxygenation in the early stages of opioid exposure during its withdrawal with subsequent correction.

When conducting our research, we used 78 white sexually mature outbred male rats, weighing 160-200 grams, which were injected intramuscularly with the drug «Nalbuphine» for 42 days. The number of platelets, prothrombin

time, prothrombin index, recalcification time, total fibrinogen, hemoglobin and hematocrit value were determined in the blood of experimental animals at different times of opioid exposure.

The obtained data were tested for normality using the Shapiro-Wilk test. The non-parametric Kruskal-Wallis H test for three or more independent groups was used to determine the significance of the difference between groups, followed by post hoc analysis using Dunn's test. R v 4.0.3 and RStudio v 1.2.5042 software were used to perform statistical calculations.

During the sixth week, the changes in the correction subgroup «cancellation + pentoxifylline» – the values of the indicators were as close as possible to the values of the corresponding indicators of the control group.

Key words: coagulation hemostasis, blood oxygenation, nalbuphine, rat.

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MORPHOMETRY OF THE CORONARY OSTIA IN WOMEN: AN ANGIOGRAPHIC STUDY

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Angiographic examination of the coronary arteries – coronary angiography allows for intravital evaluation of the coronary arteries. Structural lesions of the coronary arteries are a prerequisite for developing coronary heart disease, the most common form of cardiovascular disease among women. The work aimed to carry out a morphometric analysis of coronary artery valves in women in normal conditions and under coronary artery damage, with an assessment of the relationship between age and anthropometric indicators. Angiographic images of the coronary arteries of 56 normal women and those with structural lesions of the coronary arteries served as materials and methods. Used methods: coronary angiography, mathematical and statistical calculations. In women with lesions of the coronary arteries, the height of the left coronary artery ostia (4.78 ± 1.16 mm) exceeded the height of the right coronary artery ostia (3.94 ± 0.98 mm) ($p=0.003$). Similar differences were found in women without lesions of the coronary arteries, in particular, the height of the left coronary artery ostia was 5.96 ± 0.91 mm, the height of the right coronary artery ostia was 4.58 ± 1.10 mm ($p<0.0001$). The height of the ostia of the left ($p=0.0001$) and right ($p=0.027$) coronary arteries prevailed in healthy patients, compared to the group with coronary artery lesions. According to the analysis of the combined effect of several factors on the height of the coronary artery valves, it was established that with increasing age, height ($r=-0.35$, $p=0.047$) and body surface area ($r=-0.37$, $p=0.035$) decreased. Height was directly correlated with body weight ($r=+0.36$, $p=0.043$). According to the results of the paired correlation, a direct correlation of average strength between height and body weight ($r=+0.49$, $p=0.014$) and body surface area ($r=+0.63$, $p=0.001$) was proved. Thus, with the help of the angiographic method of research, various relationships between the height of the coronary artery ostia and the age-anthropometric parameters in women with coronary artery lesions and under normal conditions were established.

Key words: coronary artery, aorta, coronary angiography, coronary heart disease, angiography.